Indian Journal of Chemistry
Vol. 36B, March 1997, pp. 216-219

Rapid Communication

An efficient synthesis of 1,2,4-oxathiazoles from N-acylthiourea derivatives

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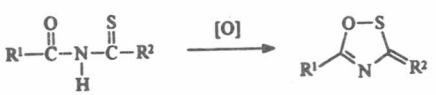
Received 4 November, 1996; accepted 26 February 1996

1,2,4-Oxathiazoles have been synthesized from their precursors, the *N*-acylthioureas by oxidative cyclization reaction. Ring structure and the charge distribution above the ring have also been studied.

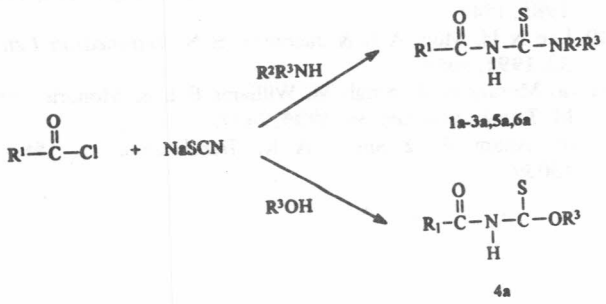
The chemistry including synthesis of 1,2,4-oxathiazoles and elucidation of their structures have not been studied well. On the contrary, ring compounds with analogous structures have been studied in detail[1], and some of them found to possess a certain degree of biological activities[2]. By reviewing the ring structure of 1,2,4-oxathiazoles, one may expect that these compounds should also exhibit a comparable degree of biological activities as other classes of heterocycles with similar structures do. We therefore thought of interest to develop a convenient and general synthetic route for this class of compounds.

Our preliminary results on the synthesis of 1,2.4-oxathiazoles by the oxidative cyclization[3] of the corresponding *N*-acylthiourea derivatives, as depicted in Scheme I, are reported in this note.



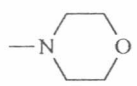
Scheme I

The required *N*-acylthiourea derivatives **1a-6a** were prepared from the reaction of acid chlorides with sodium thiocyanates and subsequent reaction with appropriate 1° or 2° amine as depicted in Scheme II. When alcohol such as ethanol was used instead of the amine, it gave the thiocarbamates compounds(Scheme II).Hydrogen peroxide and bromine were used as oxidants for the oxidative cyclization of *N*-acylthioureas under various conditions. Bromine appeared to be more feasible



1a-3a,5a,6a

4a

Compd	R^1	R^2	R^3
1a	C_6H_5	H	C_6H_5
2a	C_6H_5	H	$(m NO_2)C_6H_5$
3a	C_6H_5	CH_3	C_6H_5
4a	C_6H_5	—	C_2H_5
5a	C_6H_5		
6a	C_6H_5O	H	C_6H_5

Scheme II

oxidant than hydrogen peroxide which has been used as an oxidizing agent in the preparation of 3,5-disubstituted-1,2,4-oxathiazolines[4]. 1,2,4-oxathiazoles **1b-5b** were prepared by the bromine oxidation reaction of **1a-5a**. Hydrogen peroxide brought about the replacement of sulphur atom on thiocarbonyl group of the *N*-acylthiourea derivative **1a** by an oxygen atom to form the *N*-acylurea derivative **1c**. It also attacked the more nucleophilic carbonyl centre of compound **6a** which led to disintegration, thus preventing the formation of O-S bond that was necessary for the ring formation in both the cases (Figure 1).

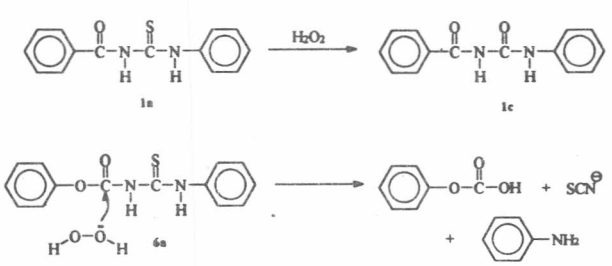
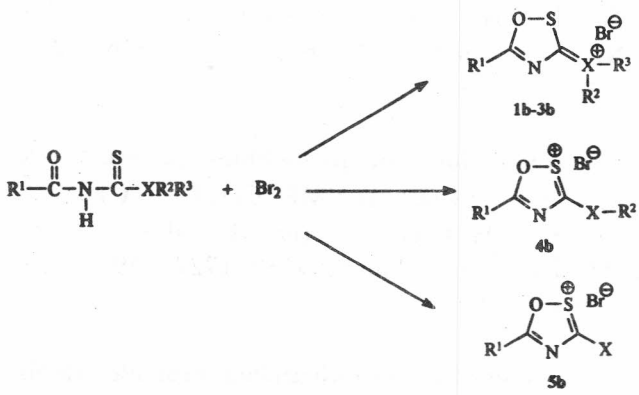
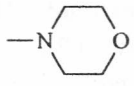


Figure 1



Compd	R^1	R^2	R^3	X
1b	C_6H_5	H	C_6H_5	N
2b	C_6H_5	H	$(m NO_2)C_6H_5$	N
3b	C_6H_5	CH_3	C_6H_5	N
4b	C_6H_5	C_2H_5	-	O
5b	C_6H_5	-	-	

Scheme III

Bromine reaction allowed a smooth conversion of **1a-5a** to the corresponding target ring molecules **1b-5b**, but failed with that bearing the phenyl formoyl group (**6a**) (*c.f.* Scheme III). The proposed mechanism for the oxidative cyclization reaction involves the initial abstraction of a hydride from NH group, followed by attack of the oxygen atom of acyl group upon the less electronegative sulphur atom of the thiocarbonyl bond to form O-S bond with the elimination of central NH proton (Figure- 2). We found that when diethylamine, a moderate organic base, was added to the reaction mixture, it

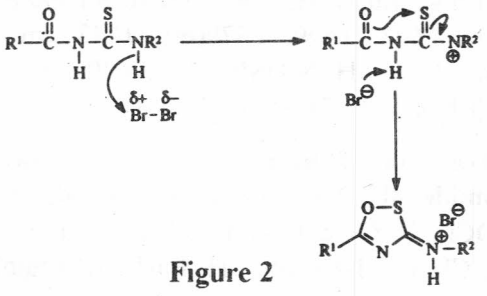


Figure 2

was possible to synthesize the 1,2,4-oxathiazole with much greater ease. Addition of diethylamine facilitates the removal of the NH proton and thus makes the cyclization step proceed easier. Another advantage of the base-catalysed cyclization reaction is that it avoided the clumsy separation process which was usually required after the addition of bromine. This is because during the reaction the base is converted to its salt, the diethylammonium bromide, which is readily soluble in water but not in the organic solvent, and hence the final product can be obtained by simple extraction with an organic solvent.The structures of the ring products were determined from their ^{1}H NMR and IR spectra. All the 1,2,4-oxathiazoles synthesized were obtained in their salt forms. Their solubility properties were quite similar except for compound **5b** that was soluble in water. Their melting points were higher than the corresponding *N*-acylthiourea or thio-carbamate derivatives. This can be attributed to the attractive force between the opposite charges in the products. There are two tautomeric forms in which the ring can exist (Figure 3), the positive charge can be located either in the endo or exocyclic position. So far there has been no evident to conclude as to which of the two forms is more stable.

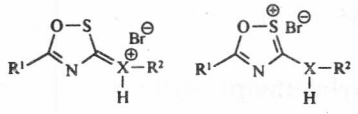


Figure 3

In conclusion, the use of bromine as an oxidizing agent allowed us to achieve a great success in the synthesis of the 1,2,4-oxathiazolium compounds with reasonable yields. We are still investigating on the synthesis of 1,2,4-oxathiazoline compounds especially those which are more soluble in water by placing different substituents in ring.

Experimental Section

^{1}H NMR spectra were recorded in $CDCl_3$ or in acetone-d_6 on a Hitachi R-1200 instrument. CHN analyses were performed on a Leco CHN-9000 instrument. IR spectra were recorded on a Bomem MB-120 Fourier-Transform infra-red spectrometer.

Synthesis of the thiourea derivatives 1a-3a,5a-6a and thiocarbamate derivative 4a. *General procedure.* A solution of sodium thiocyanate (4.05g, 50mmoles) in acetone (50mL) was slowly added dropwise at 0°C to an acid chloride (50mmoles) in acetone (20mL) with continuous stirring. The mixture was filtered using Celite on filter paper. The filtrate was slowly added at room temperature to an amine or alcohol (50mmoles) in acetone (20mL) with continuous stirring. Thereafter, two-third of the solvent was distilled under vacuum. The concentrate was left overnight in a fridge. Crystals formed were collected and dried in vacuum.

***N*-Benzoylphenylthiourea 1a.** Yield 87%, m.p. 131-32° ; ^{1}H NMR ($CDCl_3$, 20°C): δ 7.59 (m, 10H, C_6H_5), 9.24 (br, 1H, NH), 12.53 (br, 1H, NH); IR (nujol mull): 3281, 1669, 1606, 1581 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.50; H, 4.70; N;10.95. Found: C, 65.50; H, 4.65; N, 10.95%.

***N*-Benzoyl-(3-nitro)phenylthiourea 2a.** Yield 79%, m.p. 175-76°; ^{1}H NMR ($CDCl_3$, 20°C): δ 7.24-7.91 (m, 9H, C_6H_5), 9.04 (br, 1H, NH), 12.51 (br, 1H, NH); IR (nujol mull): 3267, 3150, 1653, 1582, 1541, 1533, 1509, 1321 cm^{-1}. Anal. Calcd for $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.70; N, 13.95. Found: C, 55.75; H, 3.50; N, 13.75%.

***N*-Benzoylmethylphenylthiourea 3a.** Yield 71%, m.p. 139-40°; ^{1}H NMR ($CDCl_3$, 20°C): δ 3.75 (s, 3H, CH_3), 7.25-7.59 (m, 10H, C_6H_5), 8.61 (br, 1H, NH); IR (nujol mull): 3375, 3215, 3190, 1698, 1600(m), 1585, 1515(m) cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.65; H, 5.20; N, 10.35. Found: C, 66.33; H, 5.12; N, 10.30%.

***N*-Benzoylethylthiocarbamate 4a.** Yield 75%, oily liquid at room temperature; ^{1}H NMR ($CDCl_3$, 20°C): δ 1.3-1.5 (t, 3H, CH_3), 4.4-4.8 (q, 2H, CH_2), 7.3-8.4 (m, 5H, C_6H_5), 9.6 (br, 1H, NH); IR (nujol mull): 3270,1972, 1695, 1507, 1276, 1194 cm^{-1}. Anal. calcd for $C_{10}H_{11}NO_2S$: C, 57.40; H, 5.30; N,6.70. Found: C, 57.55; H, 5.25; N, 6.55%.

Benzamidothiomorpholinoate 5a. Yield 86%, m.p. 140-42°; ^{1}H NMR ($CDCl_3$, 20°C): δ 3.6-3.8 (m, 8H, CH_2), 7.4-8.0 (m, 5H, C_6H_5), 8.6 (br, 1H, NH); IR (nujol mull): 1680, 1597, 1516, 1233, 1188, 1088 cm^{-1}.

***N*-(Phenylformaoyl)phenylthiourea 6a.** Yield 91%, m.p. 158-60°; ^{1}H NMR ($CDCl_3$, 20°C): δ 7.2-7.7 (m, 10H, C_6H_5), 8.8 (br, 1H, NH), 11.1 (br, 1H, NH); IR (nujol mull): 3150, 1727, 1594, 1223, 1136 cm^{-1}.

Synthesis of 1,2,4-oxathiazolium bromides 1b-5b. *General procedure*. A solution of bromine (2.16 g, 13.5mmoles) in chloroform (20mL) was added dropwise at 0°C to the thiourea- or thiocarbamate derivative (13.5mmoles) in chloroform (50mL) with continuous stirring. The mixture was left to stand at room temperature for 1/2 hr and the solvent distilled off under vacuum. The product was recrystallized from chloroform. The crystals or powder formed were collected and dried under vacuum.

3-Anilino-5-phenyl-1,2,4-oxathiazolium bromide 1b. Yield 78%, m.p. 201-2°; ^{1}H NMR ($CDCl_3$, 20°C): δ 7.2-8.5 (m, 10H, PhH); IR (nujol mull): 3345, 1618, 1530, 1282 cm^{-1}. Anal. Calcd for $C_{14}H_{11}N_2OSBr$: C, 50.15; H, 3.30; N, 8.35. Found: C, 50.20; H, 3.20; N, 8.45%.

3-(3-Nitroanilino)-5-phenyl-1, 2, 4-oxathiazolium bromide 2b. Yield 43%, m.p. 225-27°; ^{1}H NMR ($CDCl_3$, 20°C): δ 12.3-13.5 (b, PhH); IR (nujol mull): 3415, 1728(w), 1616, 1429, 1492(s), 1315, 1242(m) cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_3O_3SBr$: C, 44.30; H, 2.65; N, 11.05. Found: C, 44.75; H, 2.60; N, 10.80%.

3-(N-Methyl-N-phenylamino)-5-phenyl-1,2,4-oxathioazolium bromide 3b. Yield 75%, m.p. 167-68.5°; ^{1}H NMR ($CDCl_3$, 20°C): δ 4.0 (s, 3H, CH_3), 7.41-8.42 (m, 10H, PhH); IR (nujol mull): 3100, 3000, 1697, 1599, 1579(m), 1543 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_2OSBr$: C, 35.40; H, 2.55; N, 5.50. Found: C, 34.85; H, 2.55; N, 5.50%.

3-Ethoxy-5-phenyl-1,2,4-oxathiazolium bromide 4b. Yield 68%, oily liquid; ^{1}H NMR ($CDCl_3$, 20°C): δ 1.1-1.4 (t, 3H, CH_3), 3.9-4.5 (q, 2H, CH_2), 7.1-8.4 (m, 5H, PhH); IR (nujol mull):

3251, 1762, 1676, 1462, 1265, 1206 cm^{-1}. Anal. Calcd for $C_{10}H_{10}NO_2SBr$: C, 41.70; H, 3.50; N, 4.85. Found: C, 41.40; H, 3.55; N, 4.90%.

3-Morpholino- 5 -phenyl- 1, 2, 4-oxathiazolium bromide 5b. Yield 86%, oily liquid; ^1H NMR ($CDCl_3$, 20°C): δ 3.6 (s, 8H, CH_2), 7.4 (s, 5H, PhH); IR (nujol mull): 2968, 2856, 1626, 1538, 1440, 1271, 1118 cm^{-1}.

Acknowledgment

This research was supported by the City University of Hong Kong. We grateful Mr C P Benz Chan and Mr H Y John Lai for their help in our research.

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